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Homoallylic sterol/indium(III) Lewis acid: a novel enantioselective allylation system exhibiting α-regioselectivity†

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Abstract—A homoallylic sterol/indium(III) Lewis acid reagent system was utilized for the enantioselective and α-regioselective allylation of various aldehydes.

The development of new highly enantioselective C–C bond formation methods is an enduring task for organic chemists.[2] In this respect, extensive efforts have been devoted to the exploration of chiral reagents and catalysts for the carbonyl–allylation and carbonyl–ene reactions, since the resulting homoallylic alcohols are versatile building blocks for the synthesis of many natural products and pharmaceuticals.[3] Although prominent progress in this area has been achieved during the last two decades, the situation that almost all existing allylation methods exhibit γ-regioselectivity, except in a few special cases,[4] limits access to optically active α-adduct homoallylic alcohols. This greatly decreases the efficiency of many synthetic routes. For instance, preparation of the C15–C22 homoallylic alcohol fragment in Williams and Meyer's synthesis of (+)-amphidinolide K (**1**, Fig. 1) involved tedious multistep transformations.[5] Recently, the emergence of nucleophile-transfer reactions[6] offers opportunities for the development of new enantioselective C–C bond formation methods. Herein we report a novel chiral allylation system, homoallylic sterol (**2**)/indium(III) Lewis acid, for enantioselective allyl-transfer to various aldehydes exhibiting exclusive α-regioselectivity.

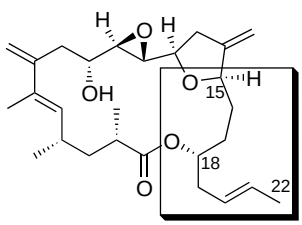
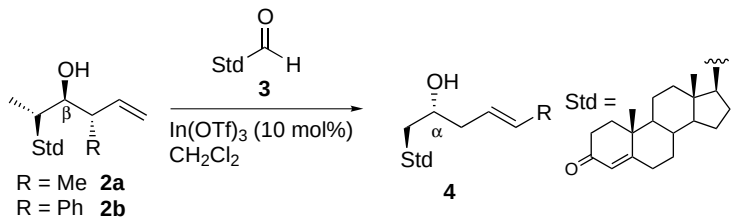


Figure 1. (+)-Amphidinolide K (**1**).

Recently, our efforts in the exploration of indium(III) Lewis acids[7] led to the discovery of an α-regioselective allyl-transfer reaction catalyzed by indium(III) Lewis acid in this laboratory.[6e,8] It is interesting to note that transfer of the allyl fragment and chirality from γ-adduct homoallylic sterol (**2**)[9] to its parent aldehyde afforded the corresponding α-adduct with inversion of stereochemistry (Scheme 1). This was accounted for by



Scheme 1. Indium(III) Lewis acid-catalyzed allyl-transfer reaction.

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† See Ref. 1.

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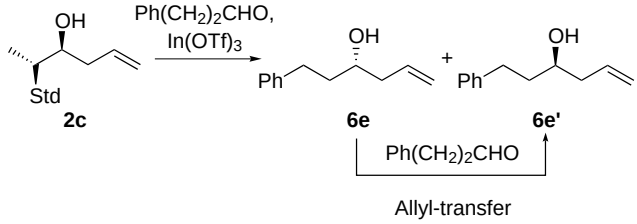
invoking a 2-oxonia[3,3]-sigmatropic rearrangement mechanism proposed by Samoshin[6f] and Nokami[6d] (Scheme 2). Thus, the utilization of γ-adduct homoallylic sterol as an allylation reagent for the transfer of its allyl fragment to other aldehydes appears to be a promising method for an enantioselective α-regioselective allylation.

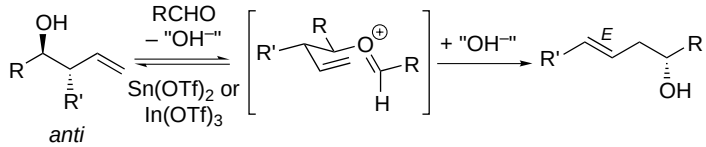
In our initial studies, a solution of **2a**[10] (0.4 mmol, 1 equiv.) and 3-phenylpropanal (0.48 mmol, 1.2 equiv.) in dichloromethane was stirred at room temperature, in the presence of a catalytic amount of $In(OTf)_3$ (10 mol%), overnight. The desired α-homoallylic alcohol **6a** was isolated in 54% yield, and in at least 98% ee as determined by chiral stationary phase HPLC employing a Daicel Chiralcel OD column (entry 1). The double bond was also found to be exclusively of the *E* geometry. Nonetheless, a small amount of the self-transfer side-product **4a** was observed and thus, subsequent reactions were conducted at −30°C instead. The allyl-transfer from **2a** to benzaldehyde (entry 2) gave a slightly lower yield of the α-adduct **6b**, though with identical excellent enantio- and *E*/*Z* selectivity. In addition, no self-transfer was observed in this case (Table 1).

Upon changing to the cinnamyl bromide derivative **2b** as the chiral allyl donor, similar stereoselectivities were obtained. Again, no self-transfer product **4b** was obtained in both instances. More importantly, both 3-phenyl-propanal and benzaldehyde (entries 3 and 4, respectively) afforded the α-adducts **6c** and **6d** in much higher yields than in the case of the analogous crotyl-transfer. This could be because the release of steric strain is greater in the case of **2b** than in **2a**. Also, the conjugated internal cinnamyl motif in the resulting α-adducts is thermodynamically more stable than the isolated terminal double bond in **2b**, providing for greater driving force toward the direction of the desired α-adducts **6**.

With the success in crotylation and cinnamylation, we explored the allyl-transfer from sterol **2c** to hydrocinnamaldehyde. It is interesting to note however that the reaction exhibited significantly lower enantioselectivity. In addition, prolonged reaction times led to lower enantioselectivities as well (62% ee at 2 h, 56% ee at 4 h, 50% ee at 8 h and 46% ee at 20 h).[11] This observation can be explained by the involvement of a second competing [3,3]-sigmatropic rearrangement leading to allyl-transfer from **6e** to hydrocinnamaldehyde (Scheme 3).[12]

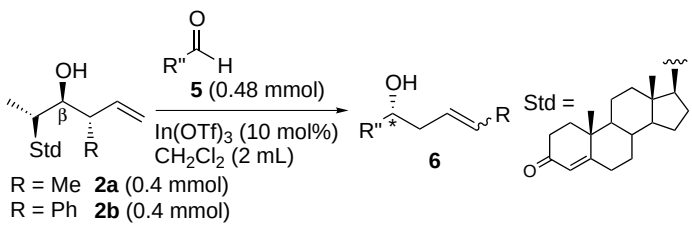


Scheme 3.



Scheme 2. Reaction pathway of the allyl-transfer reaction.

Table 1. Allyl-transfer from γ-adduct 22β-sterol **2** to various aldehydes **5**[a]



Entry	γ-Adduct	**5** R″	*T* (°C)	α-Adduct **6**	
				Yield[b] (%)	*R*:*S*[c] (*E*/*Z*)[d]
1	**2a**	$PhCH_2CH_2$	25	**6a**, 54[e]	1:99 (*E*)
2	**2a**	Ph	−30	**6b**, 49	99:1 (*E*)
3	**2b**	$PhCH_2CH_2$	−30	**6c**, 72	1:99 (*E*)
4	**2b**	Ph	−30	**6d**, 73	99:1 (*E*)

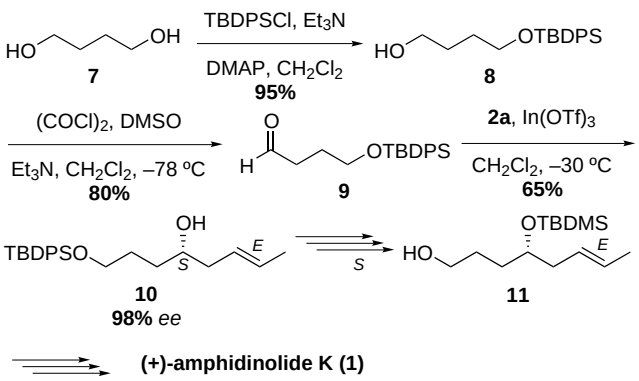
[a] Reactions were performed with **2** (0.4 mmol, 1 equiv.), **5** (0.48 mmol, 1.2 equiv.) and $In(OTf)_3$ (10 mol%) in CH_2Cl_2 (2 mL).
[b] Isolated yield with respect to the limiting reagent, γ-adduct **2**.
[c] Determined by HPLC analysis employing a Daicel Chiralcel OD column.
[d] Determined from ^1H NMR (300 MHz).
[e] A small amount of self-transfer α-adduct **4a** was observed.

This observation suggests that a Lewis acid-catalyzed allyl-transfer pathway might be an important side reaction in many enantioselective allylation reactions, which will substantially undermine the enantioselectivity.

Application of this new method to organic synthesis proved successful in the asymmetric allylation of aldehyde **9** derived from butane-1,4-diol (**7**), to give the secondary carbinol **10** in 98% ee and 65% yield (Scheme 4). Subsequent manipulations could lead to **11**, an intermediate employed in a recent total synthesis of the antitumor macrolide, (+)-amphidinolide K (**1**), in which the original route necessitated six steps in 56% yield, commencing from a known *chiral* homoallylic alcohol.

In addition, attempts were made to recover the regenerated steroidal aldehyde. Unfortunately, all efforts proved futile with the recovery of a mixture of both C20-epimers, which could be traced to the rather strong Lewis acidity of $In(OTf)_3$. To overcome this problem, a weaker indium(III) Lewis acid, $InBr_3$, was employed in this reaction instead of $In(OTf)_3$. In our studies, a solution of **2a**, benzaldehyde (0.6 mmol, 1.5 equiv.) and a catalytic amount of $InBr_3$ (0.1 equiv.) in dichloromethane was stirred for 16 h at −30°C. Upon purification by means of column chromatography, the desired α-homoallylic alcohol was isolated in 60% yield and 82% ee, together with the regenerated steroidal aldehyde without epimerization in 69% yield and 7% of recovered sterol.

In conclusion, the method was applied to the allylation of various aldehydes, and afforded α-adduct homoallylic alcohols in excellent enantioselectivity (98% ee). It was also found in the case of allyl bromide derived sterol **2c**, that absence of the allylic substituent undermines the inherent enantiospecificity of the allyl-transfer, which degrades with prolonged reaction times. This suggested that such Lewis acid-catalyzed allyl-transfers could be important side reactions in many enantioselective allylations, which will substantially erode the enantioselectivity. Studies on some known systems to verify this postulate are currently being carried out in this laboratory. In addition, the efficiency of the chiral allylation reagent **2b** has been demonstrated in the assembly of the C15–C22 fragment of (+)-amphidinolide K, where the desired enantioselectivity, regioselectivity and geometry of the double bond were obtained in a single step as predicted, in moderate yield. Last but not least, the improvement of this reagent with respect to recycling of the chiral source was explored and $InBr_3$ has shown promising results in the preliminary trials. Further studies along this line are in progress.



Scheme 4. Application to the synthesis of intermediate **10**.

Acknowledgements

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10. Prepared according to the typical procedure for indium-mediated allylation in DMF (Ref. 9), by reaction of crotyl bromide with **3**, in 56% yield (22β:22α = 99:1) and *anti*:*syn* (C22:C23) selectivity of 78:22.
11. During the course of this manuscript preparation, a similar observation was described in: Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.
12. The referee suggested an equally viable alternative viewpoint to account for the low initial ee observed in this case. Due to the absence of the allylic substituent in **2c**, the transition state for the allyl transfer (vide infra) no longer suffers from as much 1,3-allylic strain if it now adopts the alternative chair-like transition state, leading to the formation of product **6e′**.